



PATENT  
Attorney Docket No. 2481.0790-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: )  
Michael DORSCHUG et al. )  
Serial No.: 08/402,394 ) Group Art Unit: 1646  
Filed: March 10, 1995 ) Examiner: C. Saoud  
For: MINI-PROINSULIN, ITS )  
PREPARATION AND USE )

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

**TRANSMITTAL OF APPEAL BRIEF (37 C.F.R. 1.192)**

Transmitted herewith in triplicate is the APPEAL BRIEF in this application with  
respect to the Notice of Appeal filed on March 19, 1999.

This application is on behalf of

Small Entity       Large Entity

Verified Statement is:       Enclosed  
                                   Previously Filed

Pursuant to 37 C.F.R. 1.17(f), the fee for filing the Appeal Brief is:

\$155.00 (Small Entity)

\$300.00 (Large Entity)

10/20/1999 COTIN 00000122 08402394  
300.00 OP  
02 FC:120

TOTAL FEE DUE:

Appeal Brief Fee \$ 300.00

Extension Fee (if any) \$1,850.00

Total Fee Due \$2,150.00

Enclosed is Check No. 26530 in the amount of \$2,150.00.

PETITION FOR EXTENSION. If any extension of time is necessary for the filing of this Appeal Brief, and such extension has not otherwise been requested, such an extension is hereby requested, and the Commissioner is authorized to charge necessary fees for such an extension to our Deposit Account No. 06-0916. A duplicate copy of this paper is enclosed for use in charging the deposit account.

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

By:

  
Carol P. Einaudi

Reg. No.: 32,220

Date: October 19, 1999



PATENT  
Attorney Docket No. 02481.0790-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: )  
Michael DORSCHUG et al. )  
Serial No.: 08/402,394 ) Group Art Unit: 1646  
Filed: March 10, 1995 ) Examiner: C. Saoud  
For: MINI-PROINSULIN, ITS )  
PREPARATION AND USE )

**Assistant Commissioner for Patents  
Washington, D.C. 20231**

Sir:

**APPEAL BRIEF PURSUANT TO 37 C.F.R. § 1.192(a)**

This is an appeal to the Board of Patent Appeals and Interferences from the final rejection of claims 21-23, 25-27, 31, and 33-42, in the above-referenced patent application. The appealed claims, as rejected, are set forth in the attached Appendix A. The appealed claims, as amended by the Amendment and Response Under 37 C.F.R. § 1.116, are set forth in Appendix B.

Three copies of this Appeal Brief are being filed together with the required brief filing fee of \$300.00. The period for response has been extended by the filing of a petition for a five-month extension of time and the appropriate fee concurrently herewith. Please charge any additional fees that may be due to Deposit Account No. 06-0916.

I. **REAL PARTY IN INTEREST**

As a result of assignment, the real party in interest is Hoechst Aktiengesellschaft. The assignment was recorded June 21, 1989, at Reel 5095, Frame 0575.

II. **RELATED APPEALS AND INTERFERENCES**

Appellant knows of no other appeal or interference that will directly affect, be directly affected by, or have a bearing on the decision of the Board of Patent Appeals and Interferences in this appeal.

III. **STATUS OF CLAIMS**

Claims 21-23, 25-27, 31, and 33-42 are currently pending on appeal. Claims 1-10 were originally filed on June 21, 1989 in the grandparent application, Serial No. 07/369,686, claiming priority to German Application No. P38 21 159.9 filed June 23, 1988. Claims 2-5 were canceled by an amendment filed on April 21, 1992, and claims 11-13 were added. On December 2, 1992, claim 11 was canceled and claims 14 and 15 were added. A Rule 62 continuation of this application was filed on June 23, 1993 and assigned Serial No. 08/080,060 with claims 1, 6-10, and 12-15 pending. On March 25, 1994, claims 1, 6-10, and 12-15 were canceled and claims 16-30 were added. On January 13, 1995, claims 16-20, 24, and 28 were canceled and claim 21 was amended.

Following an Advisory Action mailed February 14, 1995, the present Rule 62 Continuation was filed on March 10, 1995, and assigned Serial No. 08/402,394. On November 6, 1995, claims 29-30 were canceled.

After receiving the Advisory Action mailed on August 21, 1996, Applicants filed a Request for Reconsideration After Final under 37 C.F.R. §1.129(a) on October 2, 1996. Claim 31 was added by an amendment filed concurrently with this request. Claim 32 was added by an amendment filed on June 6, 1997 and canceled on March 2, 1998.

The Final rejection of claims 21-23, 25-27, and 31 resulted in a second Request for Reconsideration After Final under 37 C.F.R. §1.129(a) filed on September 22, 1998. The amendment filed concurrently with this request added claims 33-42. The subject matter of newly added claims 33-42 was that of the original claims filed in the grandparent application. The subject matter of the pending claims in this appeal, claims 21-23, 25-27, 31, and 33-42, have been finally rejected numerous times throughout the course of prosecution. Therefore, a Notice of Appeal was filed on March 19, 1999.

#### IV. STATUS OF AMENDMENTS

All amendments to the claims have been entered, except for the Amendment After Final filed concurrently with this Appeal Brief, which amended claim 40, thereby obviating the rejection of claims 40 and 41 as non-enabled. Appendix A to this Brief contains the claims which were pending prior to the filing of the Amendment After Final.

Appendix B contains the rejected claims as amended in the concurrently filed Amendment After Final. Because the Amendment of claim 40 reduces the issues on appeal, we will present the Argument section in view of the claims in Appendix B.

**V. SUMMARY OF INVENTION**

The claimed invention relates to a novel mini-proinsulin that comprises a **full-length, unshortened B-chain** that is linked to the A-chain via only a single Arginine amino acid residue. This mini-proinsulin has the formula I

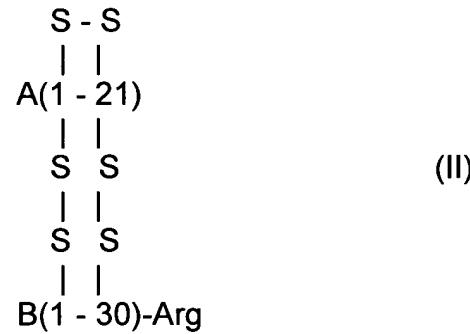
B(1-30) - Arg - A(1-21).

The mature form of insulin is easily formed from this mini-proinsulin without difficult or laborious chemical reactions. (Specification, page 1, lines 4-8 and 22-26.)

In fact, because very little of the side product, Des-B30 insulin, is formed upon cleavage of the claimed mini-proinsulin, the conversion of this mini-proinsulin to mature insulin can be accomplished by cleavage in a single reaction vessel without the need for isolation of intermediates between cleavage reactions. (Specification page 4, line 36, to page 5, line 12.) In other words, unlike the prior art processes of obtaining human insulin from proinsulin constructs, the enzyme cleavage of Appellants B(1-30)-Arg-A(1-21) mini-proinsulin with trypsin and carboxypeptidase B, or enzymes having similar action, may be accomplished simultaneously in the same reaction vessel

without having to isolate the intermediate product of the trypsin reaction before cleavage by the carboxypeptidase B enzyme.

The invention also relates to the formation of mono-Arg-insulin having the formula II



from the mini-proinsulin of formula I.

Claims 21, 25, and 39 are directed to methods of preparing mono-Arg-insulin of formula II comprising expressing a DNA sequence encoding a mini-proinsulin compound of the formula B(1-30)-Arg-A(1-21) in a bacterium. These claims are supported by the specification at page 2, lines 7-20; page 4, line 36 - page 5, line 12; and, page 13, line 19 - page 16, line 8.

Claim 42 is directed to a method of preparing mono-Arg-insulin of formula II comprising expressing a DNA sequence encoding a mini-proinsulin compound of the formula B(1-30)-Arg-A(1-21) in yeast. This claim is supported by the specification at page 2, lines 7-20; page 4, line 36 - page 6, line 14; and, page 17, line 14 - page 21, line 30.

Claims 22, 23, 26, 27, 31, 40, and 41 are directed to methods of preparing insulin comprising expressing a DNA sequence encoding a mini-proinsulin compound of the formula B(1-30)-Arg-A(1-21) in a bacterium. These claims are supported by the specification at page 4, line 36 - page 5, line 12; page 16, line 9 - page 17, line 13; and, page 21, line 31 - page 22, line 6.

Claim 38 is directed to a method of preparing a compound of formula B(1-30)-Arg-A(1-21) by expressing a DNA sequence encoding that compound in a bacterium. This claim is supported by the specification at page 2, lines 21-28; page 11, line 17 - page 14, line 8; and, page 17, line 14 - page 20, line 20.

Claims 33, 34, 35, 36, and 37 are directed to a compound of formula B(1-30)-Arg-A(1-21), a nucleic acid sequence encoding that formula, a vector with the nucleic acid sequence, a host cell with the nucleic acid sequence, and a fusion protein comprising formula B(1-30)-Arg-A(1-21), respectively. These claims are supported by the specification at page 1, lines 22-31; page 2, line 28 - page 3, line 6; and page 12, lines 7- page 13, line 18.

## VI. ISSUES

- A. Whether claims 40-41 are patentable under 35 U.S.C. § 112, first paragraph;

- B. Whether claims 21 and 33-36 are patentable under 35 U.S.C. §103(a) over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen (EPO 163,529) in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684), and Grau (U.S. Pat. No. 4,639,332);
- C. Whether claims 25 and 37-38 are patentable under 35 U.S.C. §103(a) over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen (EPO 163,529) in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684), and Grau (U.S. Pat. No. 4,639,332) and further in view of Mai et al. (U.S. Pat. No. 5,087,564);
- D. Whether claims 22 and 23 are patentable under 35 U.S.C. §103(a) over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen (EPO 163,529) in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684), and Grau (U.S. Pat. No. 4,639,332).
- E. Whether claims 26-27 and 31 are patentable under 35 U.S.C. §103(a) over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen (EPO 163,529) in view of Goeddel et al. (EPO 055,945), Man et al, Grau (U.S. Pat. No. 4,801,684), and Grau (U.S. Pat. No. 4,639,332); and
- F. Whether claims 39 and 42 are patentable under 35 U.S.C. §103(a) over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen (EPO 163,529) in view of Grau (U.S. Pat. No. 4,801,684), and Grau (U.S. Pat. No. 4,639,332).

**VII. GROUPING OF CLAIMS**

Pursuant to 37 C.F.R. § 1.192(c)(7), independent claims 21, 22, 25, 26, 31, 33, 37, 39, 40, and 42 and dependent claims 23, 27, 34-36, 38, and 41 stand or fall together, as argued. Appellants have argued the issues set forth by the Examiner separately. However, the common subject matter to every pending claim is the compound of formula B(1-30)-Arg-A(1-21). And, because the prior art fails to render this compound and its use obvious, for the reasons that will be explained below, all the pending claims should stand together.

**VIII. ARGUMENT**

A. The Examiner has rejected claims 40-41 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains of with which it is most nearly connected, to make and/or use the invention.

In particular, the Examiner states that claims 40-41 are directed to a method of making mono-Arg-insulin of formula II, but the method includes an additional cleavage step, which would result in formation of insulin rather than mono-Arg-insulin.

Appellants have filed an Amendment under Rule 1.116 amending claim 40 to read as follows:

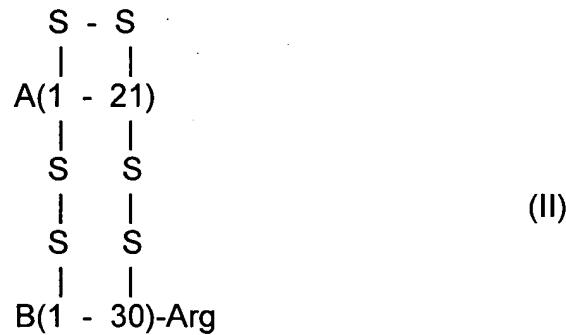
A method for the preparation of human insulin comprising:

- a) expressing a DNA sequence encoding the compound of formula I

B(1-30)-Arg-A(1-21) (I)

in a bacterium;

b) cleaving the expressed compound of step (a) with trypsin resulting in the compound of the formula II



wherein A(1-21) and B(1-30) denote the A and B chains of human insulin and the -S-S- bridges are positioned as in insulin; and

(c) cleaving the resulting compound of step (b) with carboxypeptidase B.

In view of this amendment, the premise upon which the Examiner's rejection is based has been obviated. Therefore, Appellants request that this rejection be withdrawn.

B. The Examiner has rejected claims 21 and 33-36 under 35 U.S.C. § 103 as allegedly being unpatentable over the Markussen references (U.S.P. 4,916,212 ('212') and EPO 163,529 ('EPO')), in view of Goeddel et al. and the Grau references (U.S.P. 4,801,684 ('684') and U.S.P. 4,639,332 ('332')). The Examiner contends that

Markussen et al. ('212) discloses insulin precursors of the form B(1-29)-X<sub>n</sub>-Y-A(1-21), that X is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and "Y" is Lys or Arg. The Examiner further states that X is preferably selected from the group consisting of Ala, Ser, and Thr. Moreover, the Examiner contends that the amino acid at position 30 in native human insulin is Thr and that this position is equivalent to the "X" of Markussen.

The Examiner further notes that this precursor protein is a single peptide chain that is converted to human insulin by derivatization and treatment with trypsin. It is also the Examiner's contention that fusion proteins and their cleavage from the precursor are disclosed, and that a DNA sequence encoding the insulin precursor, expression vectors, transformed cells, and recombinant methods of production in yeast as well as *E. coli* holding plasmids encoding the desired insulin precursors are also disclosed and claimed. The Examiner asserts that Markussen 'EPO' teaches essentially the same invention but admits that both Markussen references do not specifically teach the preparation of mono-Arg-insulin or the use of trypsin as a cleavage agent for generation of mono-Arg-insulin.

The Examiner cites Goeddel et al. as teaching the production of recombinant fusion proteins of insulin precursors with another protein and cleaving them, and that the insulin variant has a C chain of six amino acids. The Examiner also states that Goeddel et al. teaches production in *E. coli*.

The Examiner cites Grau ('684) as allegedly teaching the use of trypsin and carboxypeptidase B simultaneously to produce mature insulin from proinsulin. Additionally, the Examiner cites Grau ('332) as allegedly teaching that treatment of proinsulin with trypsin alone gives intermediates with an arginine at B31, and that this derivative is allegedly stable to further tryptic degradation. According to the Examiner, enzymes having both tryptic and carboxypeptidase B activity are required to produce insulin.

The Examiner asserts that a preferred embodiment of Markussen is B(1-29)-Ser-Lys-A(1-21), and that the starting material B(1-30)-Arg-A(1-21) claimed by Appellants is an obvious variant of this preferred embodiment, especially because, in the Examiner's opinion, the claimed generic formula of the prior art encompasses Appellants claimed composition. Thus, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the preferred embodiment of Markussen et al. ('212) for the production of mono-Arg-insulin as taught by Grau because mono-Arg-insulin is exceptionally stable to further tryptic degradation, which therefore, makes the mini-proinsulin an ideal and obvious choice for use in the preparation of mono-Arg-insulin.

The Examiner further contends that it would have been obvious to make fusion proteins as taught by Goeddel using the insulin precursor, DNA sequences, and vectors allegedly taught by either Markussen reference for the production of mono-Arg-insulin

of Grau and to cleave the fusion protein to release the desired protein as taught by Goeddel. It is the Examiner's position that the motivation for such proceedings is that of the allegedly known benefits of producing small peptides as fusion proteins in bacterial or yeast hosts and the success with another insulin variant having a shortened C chain and because of the usefulness of fusion proteins suggested by Markussen.

Appellants contend that the Examiner's premise that Markussen teaches the claimed B(1-30)-Arg-A(1-21) is erroneous and, therefore, each one of the Examiner's rejections B-F set forth above, which is based on that contention, is in error. In the instant claims, the mini-proinsulin composition, B(1-30)-Arg-A(1-21), is the necessary expression product that is processed in the method of preparing mono-Arg-insulin as claimed.

To establish a *prima facie* case of obviousness, an Examiner must, among other things, establish that (1) the prior art would have suggested that the ordinarily skilled artisan make the "claimed" composition; and (2) the ordinarily skilled artisan would have had a reasonable expectation of success in making the "claimed" invention from the prior art. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In this case, the prior art fails to suggest to skilled artisans that they should make the "claimed" mini-proinsulin B(1-30)-Arg-A(1-21), and that they would have had a reasonable expectation of success in carrying out the proposed modification of the insulin precursor of Markussen.

Because of these failings of the prior art, the Examiner has not met the burden of establishing a *prima facie* case.

Markussen discloses an insulin precursor represented by a generic formula B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21). This general formula of Markussen encompasses a large number of species. In fact, a simple calculation shows that this formula includes millions of possible compounds which may be used as the starting material to produce insulin.

The Examiner's contention that the substitution of Thr for Ser and Arg for Lys is merely a conservative amino acid substitution, does not provide the necessary suggestion to select this particular substitution from among the millions of possible compounds that Markussen's generic formula encompasses. Simply because the reference states what X and Y may preferably be, does not eliminate the possibility of the many other indications in the reference of what X and Y may be. No reason is provided by the Examiner as to why one should choose Thr over the other possible amino acids for X or why there should only be a single amino acid at the X position.

The Examiner has pointed out that the preferred amino acids at the X position are Lys, Arg, and Thr, and that a preferred compound of the generic formula is B(1-29)-Ser-Lys-A(1-21). Moreover, the Examiner has asserted that substitution of Thr and Arg for X and Y respectively is merely a conservative amino acid substitution.

Appellants would respectfully point out that the other preferred compounds specifically referenced by Markussen are B(1-29)-Ala-Ala-Lys-A(1-21), B(1-29)-Thr-Arg-Glu-Ala-Glu-Asp-Leu-Gln-Lys-A(1-21), and B(1-29)-Thr-Arg-Glu-Ala-Glu-Asp-Leu-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln-Lys-A(1-21). Of particular significance is that when Thr is in the X position, 8 or 30 additional amino acids form part of the connecting C -chain. Moreover, not a single one of Markussen's preferred constructs have a C-chain that ends with Arg instead of Lys.

Based on the complete disclosure of the preferred constructs in Markussen, if Thr were selected for the X position, there would need to be several more amino acids in the C chain, not just a single Lys or Arg residue. Moreover, it does not appear that the skilled artisan would have been led to the selection of Arg as the final amino acid in the C-chain based on Markussen's disclosure, as a conservative amino acid substitution, in view of the fact that Markussen's examples never include such a selection. Thus, even in view of the preferred precursors disclosed in Markussen, unless one knew the exact composition disclosed in the instant specification in advance, there would be no incentive to achieve this claimed composition from among the many precursor compositions encompassed by the general formula having preferred amino acid selections for X and Y.

Moreover, a review of the prosecution history of Markussen '212, which forms a part of the public record for this patent<sup>1</sup>, reveals that Markussen never contemplated Appellants' claimed B(1-30)-Arg-A(1-21) mini-proinsulin, and, in fact, teaches away from Appellants' claimed mini-proinsulin construct. The prosecution history of the '212 patent evidences that modification of the general formula suggested by the Examiner would destroy the intended function of the insulin precursor of Markussen's invention.

Notably, the B chain of Markussen is 29 amino acids in length. The  $(X_n \cdot Y)_m$  portion of Markussen's generic formula for mini-proinsulin is the connecting C chain that is excised from the peptide during processing to achieve the B30 Thr esters which are subsequently converted to human insulin. Throughout the prosecution of the '212 patent Markussen emphasizes that his B chain is a shortened B chain.

In Markussen's October 24, 1988 response (Appendix C at 170), it was argued that

applicants' human insulin precursors are unobviously advantageous. . . in that they may be converted in high yield through [transpeptidation] of the insulin precursors into Thr B30 esters of human insulin, and then into human insulin by the process of Markussen 4,343,898.

At page 10 of the October response (Appendix C at 172, Markussen states that [a]pplicants already know that a wide variety of insulin-like compounds of formula 1 in 4,343,898 convert into human insulin . . . , which list includes human

---

1

For ease of use by the Examiner and Board, the Markussen '212 prosecution history is attached hereto as Appendix C. The page references in this appeal brief refer to the numbers in the lower right-hand corner.

proinsulin, they looked to discovering human insulin precursors that can be generated by a transformed yeast in high yield.

In Markussen's response filed July 13, 1989 (the July response), it was stated at page 5 (Appendix C at 187) that

[a]pplicants' are entitled to rely on the consensus in the art that the C-chain serves nothing more than a spacing function. The C-chain bridges the A and B chains and aligns them into the proper insulin configuration. At sometime thereafter the C-chain is excised.

At page 6 of the July response (Appendix C at 188), Markussen emphasizes that the insulin precursor of the claimed invention lacks the B30 Threonine residue present in human insulin stating

[t]he insulin precursor formula set out in Applicants' claims names the B(1-29) chain, which is a shortened B-chain of human insulin. **The B30 residue (Thr) present in human insulin is not there.** . . . (Emphasis added.)

Moreover, at page 8 (Appendix C at 190), Markussen states that the Examiner is unable to incorporate any practice of Applicants' invention within the metes and bounds of Goeddel, [the prior art]. Within the scope of Goeddel, there are too many variations that are not Applicants' invention, the paired basic amino acid residues in particular and presence only of B(1-30). . . . Applicants' invention [B(1-29)] is not taught nor is it somehow exemplified.

At page 9 (Appendix C at 191), Markussen continues his argument pointing that the novelty of his invention is not suggested by the prior art because there is no teaching or suggestion in that art of a B(1-29) chain. Rather, the art includes a B(1-30) chain, which Markussen argues "in theory" might result if "Applicants' (X<sub>n</sub>-Y) bridging

chain is a peptide which commences with Thr . . ." However, Markussen continues that

[g]ood reason exists for absence of even the narrow (hypothetical) overlap between the proinsulin analogs of Applicants and [the prior art] urged by the Examiner. The overlap region must satisfy two different approaches to excision of the bridging chain. The [prior art technique] employs the paired basic amino acid residues that allow excision of the bridging chain in facile fashion.

**Applicants employ the transpeptidation technology of Markussen 4,434,898 on the B(1-29)-(X<sub>n</sub>-Y)-A(1-21). (Emphasis added.)**

Appendix C at 192.

Finally, in the Examiner's reasons for allowance of the '212 patent, upon which Markussen did not comment, it was stated that "[a]pplicants have further pointed out several features which contribute to the superiority of the precursors of the instant invention which are not anticipated or suggested by the [prior art]. These features are the length of the B chain in the instant invention . . ." (Appendix C at 198.)

Thus, in view of the foregoing remarks from the prosecution history, it is clear that a B(1-30) chain is not contemplated by Markussen. And, any suggestion to modify the B chain to B30 before the transpeptidation disclosed in Markussen is expressly distinguished by Markussen as not being within the scope of the invention. Furthermore, even if Thr were hypothetically in the X position, Markussen teaches that this Thr is part of the bridging C chain and would, therefore, be excised upon transpeptidation and then Thr would be inserted into the B30 position. In other words, Thr at the X position is not equivalent to a B(30) Thr. Thus, a modification of

Markussen to render the X position equivalent to the B(30) position would destroy the ability of the precursor to be used as contemplated by Markussen in the transpeptidation reaction.

Based on Markussen's disclosure which must include the limitations of the prosecution history, the skilled artisan would have had no reasonable expectation of success in achieving Appellants' claimed B(1-30)-Arg-A(1-21) compound. To use Appellants' specification as a template for its own reconstruction in the manner that the Examiner has done is an inappropriate process by which to determine patentability.

*Sensonics, Inc. v Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

Appellants further contend that the Examiner's rejection is in error because it would not be obvious to obtain the mono-Arg-insulin taught by Grau from the insulin precursor set out in Markussen.

As set forth above, Markussen '212 and Markussen (EPO) discuss methods for producing proinsulin precursors of the formula B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) with the purpose of producing human insulin using the Markussen 4,343,898 process. These precursors do not have a B(30) Thr. Moreover, these precursors are taught to be converted by transpeptidation into B30 esters of human insulin and subsequently into human insulin. (See Markussen '212, column 8, lines 41-58.) As set forth previously, this transpeptidation step is a necessary step in the Markussen process to achieve Thr at the B(30) position, which is the amino acid present in natural human insulin at this

position. Without such a step, natural human insulin could not be achieved with the Markussen construct.

It is also emphasized over and over in the prosecution history of Markussen that their human insulin precursors are unobviously advantageous because they may be converted in high yield by transpeptidation which yields the L-threonine esters, and then into human insulin by the process of Markussen 4,343,898. And, at pages 11-12 of the July response (Appendix C at 193-94), Markussen states that "[e]xpression of insulin in high yield is of little use in real life without the availability of a high yield conversion procedure [such as that set forth in Markussen 4,434,898]." There would be no incentive to try to convert the B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) precursors of Markussen to the Grau mono-Arg-insulin which has the intact human insulin B chain, B(1-30) based on the Markussen's requirement that

(a) its starting material does not have B(30) Thr, and that this starting material is produced in high yield from yeast, and

(b) its starting material is converted in a transpeptidation step to form a B(30) ester, which in turn is converted to insulin in high yield.

Appellants concede that it is well-known in the art that there are numerous methods of synthesizing insulin, and that each method in turn results in the production of various intermediate products, some of which are stable like the mono-Arg-insulin that Appellants produce. However, the mere fact that Grau discloses mono-Arg-insulin

that is stable in crystalline form does not provide motivation to the skilled artisan to convert the mini-proinsulin of Markussen which lacks the intact B(1-30) human insulin B chain to a mono-Arg-insulin, particularly because Markussen notes that its precursor is produced in high yield from yeast, and is converted in a transpeptidation step to form a B(30) ester, which in turn is converted to insulin in high yield.

The Federal Circuit has expressly held, that "there must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references (emphasis added)." *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989). Moreover, the suggestion may not derive solely from appellants' disclosure. *In re Dow Chem.*, 837 F.2d 469, 473 (Fed. Cir. 1988). As has been explained above, in this case such logical reasoning which justifies the combination of Markussen and Grau is absent. The Examiner's suggested combination appears to only derive from appellant's disclosure. In view of the full disclosure of the Markussen and Grau references, it would appear that to arrive at her rejection, the Examiner picked and chose only so much of the prior art reference as would support her position to the exclusion of other parts necessary to the full appreciation of what is fairly suggested to the ordinarily skilled artisan. This is improper hindsight analysis. See *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986).

Appellants also assert that the rejection is in error because the prior art would not have suggested to the skilled artisan to use a mono-Arg-insulin to yield human insulin. Appellants reiterate their past argument that Thim et al., Secretion and processing of insulin precursors in yeast, Proc. Natl. Acad. Sci. USA 83:6766-6770 (1983) at the paragraph bridging pp. 6769, first two sentences, informs the skilled artisan that trypsin would not cleave a mini-proinsulin with only an Arg-Arg or Lys-Arg bridge between the B and A chains.

Furthermore, Markussen's use of the transpeptidation method supports a conclusion that those skilled in the art would not have expected trypsin to cleave at the C-terminus of a bridging Arg residue in the single chain "precursor" (the Arg of the recited formula B(1-30)-Arg-A(1-21)) to ultimately generate the two chain, mature form of insulin. Why else would one go through the additional steps involved in the L-threonine ester and not discuss or even mention other more direct methods such as cleavage with trypsin? While Markussen '212 discusses cleavage, it is removal of an additional superfluous **amino acid preceding** the insulin precursor, which may have a function in protecting the insulin precursor against *in vivo* degradation in the host cell or provide information necessary for transporting the protein into the periplasmic space and across the cell wall into the medium. (See Markussen '212, at col 3, lines 52-64.) This does not, however, relate to the enzymatic cleavage step involving the generation of insulin from a single chain precursor.

Thus, the ordinarily skilled artisan would have been dissuaded from methods that use a mono-Arg-insulin to yield human insulin. The prior art teaches away from the combination the Examiner has proposed since one skilled in the art would not have expected trypsin to cleave at a single Arg residue in appellant's recited mini-proinsulin formula B(1-30)-Arg-A(1-21), resulting in formation of a two chain insulin or mono-Arg-insulin product according to the claimed invention.

Additionally, the Examiner's rejection is in error because there is no assurance and no reasonable expectation of success that the alleged teaching of Grau '684 of the simultaneous addition of trypsin and carboxypeptidase would work with the mini-proinsulin of the present invention.

Grau ('684) describes a **natural porcine proinsulin** isolated from the pancreas while the instant invention describes a mini-proinsulin of the formula B(1-30)-Arg-A(1-21).

Since it is known that trypsin cleaves at the carboxy terminus of the basic amino acids arginine and lysine, in the case of porcine proinsulin, trypsin can cleave theoretically at 6 different sites in the molecule, i.e., 2 sites in the B-chain, 3 sites in the C-chain and 1 site between C- and A- chain. Because the cutting rates (kinetics) of the possible cuts depend on the amino acid environment at each site, the actual cutting rates at the six different sites are different. In order for Grau to achieve their invention, the cutting rates at Arg-(B22) and Lys-(B29) must be relatively low compared to at least

the rate of the cutting site at Arg-(C35) since the process described by Grau ('684) yields as the main product insulin with an intact B-chain. The Arg-(C1) is cut off by carboxypeptidase B.

However, cutting off the mini-proinsulin from the fusion protein in the instant invention is at a different site from the splice site in the porcine insulin described by Grau ('684). In addition, Appellants assert that the cutting rate of trypsin at this new site could not have been predicted in view of Grau ('684).

Thus, there is nothing in the Grau '684 reference or the other prior art references of record that would suggest to the skilled artisan that the B(1-30)-Arg-A(1-21) mini-proinsulin fusion protein claimed by Appellant could be processed with the enzyme combination used in the Grau '684 reference.

For all of these reasons, appellants request that the rejection be withdrawn.

C. The Examiner has rejected claims 25 and 37-38 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Markussen references, Goeddel et al., the Grau references, and Mai et al. The Examiner states that Markussen, Goeddel et al., and Grau do not specifically teach the bridging member Met-Ile-Glu-Gly-Arg of step (A) in the claim. According to the Examiner, Mai et al. teaches that cyanogen bromide cleaves after the amino acid methionine and that Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. The Examiner further asserts that both Markussen and Goeddel et al.

suggest making fusion proteins, which can be cleaved. Thus, the Examiner concludes that it would have been *prima facie* obvious to the skilled artisan to use these common cleavage sites in fusion proteins. The Examiner further contends that there is a reasonable expectation of success because production of fusion proteins was well-known in the art at the time the invention was made.

In addition to the shortcomings addressed above, claims 25 and 37-38 are not obvious over the prior art because they include a novel and nonobvious bridging member in the fusion protein. Here, the Examiner admits that the bridging member is not taught in the prior art. Nevertheless, the Examiner concludes that Mai's disclosure would lead the skilled artisan to the use of the claimed bridging member.

Mai discloses cleavage sites in prothrombin, which are acted upon by the serine protease factor Xa at column 9. While the Mai reference discloses a proposed substrate recognition determinant of factor Xa that is Ile-Glu-Gly-Arg, the remainder of this reference never suggests using this sequence in a fusion peptide. Rather, the reference teaches use of a recA-Glu-Gly-Arg or recA-Glu sequence. There is no suggestion to add an Ile-Glu-Gly-Arg sequence to a fusion protein, much less a Met-Ile-Glu-Gly-Arg sequence as Appellants have done. Clearly, the prior art references do not reasonably provide the ordinarily skilled artisan with a vision of the claimed bridging sequence for use in the claimed fusion protein. Thus, one skilled in the art would not be led to Appellants invention based upon the teachings of Mai.

Moreover, the Examiner's rejection is in error because there is no assurance and no reasonable expectation of success that the alleged teaching of Grau '684 of the simultaneous addition of trypsin and carboxypeptidase would work with the mini-proinsulin of the present invention having the claimed bridging member. Cutting off the rest of the bridging member (IEGR) - after removal of the fusion part by CNBr - is provided by trypsin, which cuts also at other sites in the mini-proinsulin part of the fusion protein (Arg-(B22), Lys-(B29) and Arg-(C1)).

Grau ('684) describes a natural porcine proinsulin isolated from the pancreas while the instant invention describes a mini-proinsulin of the formula B(1-30)-Arg-A(1-21). The cutting off of the mini-proinsulin from the bridging member occurs at a site which has no equivalent in the porcine insulin described by Grau ('684). In addition, Applicants assert that the cutting rate of trypsin at this new site could not have been predicted in view of Grau ('684).

Thus, there is nothing in the Grau '684 reference or the other prior art references of record that would suggest to the skilled artisan that the B(1-30)-Arg-A(1-21) mini-proinsulin having the MIEGR bridging member claimed by Appellant could be processed with the enzyme combination used in the Grau '684 reference.

A determination of obviousness premised on the obvious to try standard is improper. See *In re Dow Chem.*, 837 F.2d 469, 471 (Fed. Cir. 1988); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The appropriate standard is, rather, what the prior

art would have led the skilled person to do. Consequently, in view of the fact that the prior art does not contain or suggest the knowledge of the bridging member or the use of such a bridging member with the claimed mini-proinsulin to be expressed in a bacterium, it must be concluded that the Examiner has improperly used the invention as a template for its own reconstruction. *Sensonics*, 81 F.3d at 1570.

Thus, for this additional reason, appellants request that this rejection be withdrawn.

D. The Examiner has rejected claims 22 and 23<sup>2</sup> under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Markussen references, either in view of Goeddel et al. or the Grau references. The Examiner believes it would have been obvious to use both trypsin and carboxypeptidase B to convert the mini-proinsulin of Markussen first to mono-Arg-insulin, and then to insulin. This conclusion is premised upon the Examiner's contention that Grau teaches that mono-Arg-insulin is resistant to further tryptic degradation and thus, the skilled artisan would have been motivated to use carboxypeptidase B in addition to trypsin to obtain insulin to treat diabetes.

---

2

Appellants have noted that the Examiner did not make an obviousness rejection of claims 40 and 41, but assume that if this was an oversight, the rejection would be similar to that made for claims 22 and 23. Therefore, Appellants believe that the arguments made in support of the non-obviousness of claims 22 and 23 would also apply to claims 40 and 41.

Appellants note that the arguments regarding claims 21 and 33-36 as set forth in B above provide the reasons why this rejection is in error. In summary, the prior art fails to suggest to skilled artisans that they should make the "claimed" mini-proinsulin B(1-30)-Arg-A(1-21), and that they would have had a reasonable expectation of success in carrying out the proposed modification of the mini-proinsulin of Markussen.

Markussen's invention is a B(1-29) insulin precursor that has a connecting C chain that is excised to produce an insulin precursor by a yeast cell and which would have to have the amino acid at position B30 added in a transpeptidation process.

A review of the prosecution history of Markussen '212 (Appendix C), which forms a part of the public record for this patent reveals that Markussen never contemplated Appellants' claimed B(1-30)-Arg-A(1-21) mini-proinsulin, and, in fact, teaches away from Appellants' claimed mini-proinsulin. The prosecution history of the '212 patent evidences that modification of the general formula suggested by the Examiner would destroy the intended function of the insulin precursor of Markussen's invention, i.e., to be converted in high yield to insulin via the transpeptidation process.

Moreover, just because Grau teaches that mono-Arg-insulin was known and that it is stable in a crystalline form to further tryptic degradation is insufficient motivation for modification of the Markussen method of using B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) mini-proinsulin, converting that to a B30 ester of human insulin, and subsequently converting that ester to human insulin. As set forth previously, transpeptidation is a necessary step in the

Markussen process to achieve Thr at the B(30) position, which is the amino acid present in natural human insulin at this position. Without such a step, natural human insulin could not be achieved with the Markussen construct.

Furthermore, it is emphasized over and over in the prosecution history of Markussen that their human insulin precursors are unobviously advantageous because they may be converted in high yield by transpeptidation which yields the L-threonine esters, and then into human insulin by the process of Markussen 4,343,898. And, at pages 11-12 of the July response (Appendix C at 193-94), Markussen states that "[e]xpression of insulin in high yield is of little use in real life without the availability of a high yield conversion procedure [such as that set forth in Markussen 4,434,898]."

There would be no incentive to try to convert the B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) precursors of Markussen to the Grau mono-Arg-insulin which has the intact human insulin B chain, B(1-30) based on the Markussen's requirement that

- (a) its starting material does not have B(30) Thr, and that this starting material is produced in high yield from yeast, and
- (b) its starting material is converted in a transpeptidation step to form a B(30) ester, which in turn is converted to insulin in high yield.

Thus, Appellants request that this rejection be withdrawn.

E. The Examiner has rejected claims 26-27 and 31 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Markussen references, in view of either Goeddel et al., Mai et al., or the Grau references. Again, the Examiner states that it would have been obvious to obtain the claimed mini-proinsulin in view of the Markussen disclosure. Moreover, it is the Examiner's position that it would have been obvious to add the cleavable sequence Met-Ile-Glu-Gly-Arg to the fusion proteins suggested by Markussen in view of Mai and to use both trypsin and carboxypeptidase B to convert the mini-proinsulin of Markussen et al. first to mono-Arg-insulin, and then to insulin. Further, the Examiner's asserted motivation for conversion to mono-Arg-Insulin is that Grau teaches that mono-Arg-insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. Finally, the Examiner contends that one of ordinary skill in the art would not expect the methods of Markussen and Grau for the production of insulin precursors and mono-Arg-insulin to result in the formation of substantial amounts of Des-B30 insulin, nor are there any steps in the instant claims which would distinguish the prior art in resulting in differing amounts of Des-B30 insulin, absent clear and convincing evidence to the contrary.

Appellants note that the arguments regarding claims 21 and 33-36 as set forth in VIII B above, as well as the arguments regarding claims 25 and 37-38 set forth in VIII C above, provide the reasons why this rejection is in error. In summary, the prior art fails

to suggest to skilled artisans that they should make the "claimed" mini-proinsulin B(1-30)-Arg-A(1-21), and that they would have had a reasonable expectation of success in carrying out the proposed modification of the mini-proinsulin of Markussen.

Markussen's invention is a B(1-29) insulin precursor that has a connecting C chain that is excised to produce an insulin precursor by a yeast cell and which would have to have the amino acid at position B30 added in a transpeptidation process.

A review of the prosecution history of Markussen '212 (Appendix C), which forms a part of the public record for this patent, reveals that Markussen never contemplated Appellants' claimed B(1-30)-Arg-A(1-21) mini-proinsulin, and, in fact, teaches away from Appellants' claimed mini-proinsulin. The prosecution history of the '212 patent evidences that modification of the general formula suggested by the Examiner would destroy the intended function of the insulin precursor of Markussen's invention, i.e., to be converted in high yield to insulin via the transpeptidation process.

Moreover, just because Grau teaches that mono-Arg-insulin was known and that in a crystalline form it is stable to further tryptic degradation is insufficient motivation for modification of the Markussen method of using B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) mini-proinsulin, converting that to a B30 ester of human insulin, and subsequently converting that ester to human insulin. As set forth previously, this transpeptidation step is a necessary step in the Markussen process to achieve Thr at the B(30) position, which is the amino acid

present in natural human insulin at this position. Without such a step, natural human insulin could not be achieved with the Markussen construct.

Moreover, it is emphasized again and again in the prosecution history of Markussen that their human insulin precursors are unobviously advantageous because they may be converted in high yield by transpeptidation which yields the L-threonine esters, and then into human insulin by the process of Markussen 4,343,898. And, at pages 11-12 of the July response (Appendix C at 193-94) Markussen states that "[e]xpression of insulin in high yield is of little use in real life without the availability of a high yield conversion procedure [such as that set forth in Markussen 4,434,898]."

There would be no incentive to try to convert the B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) precursors of Markussen to the Grau mono-Arg-insulin which has the intact human insulin B chain, B(1-30) based on the Markussen's requirement that

- (a) its starting material does not have B(30) Thr, and that this starting material is produced in high yield from yeast, and
- (b) its starting material is converted in a transpeptidation step to form a B(30) ester, which in turn is converted to insulin in high yield.

Furthermore, the claimed fusion proteins include a novel and nonobvious bridging member. The Examiner has admitted that the bridging member is not taught in the prior art. Nevertheless, the Examiner concludes that Mai's disclosure would lead the skilled artisan to the use of the claimed bridging member.

Mai disclosed cleavage sites in prothrombin, which are acted upon by the serine protease factor Xa at column 9. While the Mai reference discloses a proposed substrate recognition determinant of factor Xa that is Ile-Glu-Gly-Arg, the remainder of this reference never suggests using this sequence in a fusion peptide. Rather, the reference teaches use of a recA-Glu-Gly-Arg or recA-Glu sequence. There is no suggestion whatsoever to add an Ile-Glu-Gly-Arg sequence to a fusion protein, much less a Met-Ile-Glu-Gly-Arg sequence as Appellants have done. Clearly, the prior art references do not reasonably provide the ordinarily skilled artisan with a vision of the claimed bridging sequence for use in the claimed fusion protein. Thus, one skilled in the art would not be led to Appellants invention based upon the teachings of Mai.

Additionally, the Examiner's rejection is in error because there is no assurance and no reasonable expectation of success that the alleged teaching in Grau '684 of the simultaneous addition of trypsin and carboxypeptidase would work with the mini-proinsulin of the present invention having the claimed bridging member.

The mini-proinsulin of the process of the present invention is part of a fusion protein. The fusion part is connected via a bridging member (MIEGR) to the mini-proinsulin having a C-chain with just one amino acid (Arg). Cutting off the rest of the bridging member (IEGR) - after removal of the fusion part by CNBr - is provided by trypsin, which cuts also at other sites in the mini-proinsulin part of the fusion protein (Arg-(B22), Lys-(B29) and Arg-(C1)).

Grau ('684) describes a natural porcine proinsulin isolated from pancreas while the instant invention describes a mini-proinsulin of the formula B(1-30)-Arg-A(1-21).

Since it is known that trypsin cleaves at the carboxy terminus of the basic amino acids arginine and lysine, in the case of porcine proinsulin, trypsin can cleave theoretically at 6 different sites in the molecule, i.e., 2 sites in the B-chain, 3 sites in the C-chain and 1 site between C- and A- chain. Because the cutting rates (kinetics) of the possible cuts depend on the amino acid environment at each site, the actual cutting rates at the six different sites are different. In order for Grau to achieve their invention, the cutting rates at Arg-(B22) and Lys-(B29) must be relatively low compared to at least the rate of the cutting site at Arg-(C35) since the process described by Grau ('684) yields as main product insulin with intact B-chain. The Arg-(C1) is cut off by carboxypeptidase B.

However, cutting off the mini-proinsulin from the bridging member occurs at a site which has no equivalent in the porcine insulin described by Grau ('684). In addition, Applicants assert that the cutting rate of trypsin at this new site could not have been predicted in view of Grau ('684).

Thus, there is nothing in the Grau '684 reference or the other prior art references of record that would suggest to the skilled artisan that the B(1-30)-Arg-A(1-21) mini-proinsulin having the MIEGR bridging member claimed by Appellant could be processed with the enzyme combination used in the Grau '684 reference.

For all of these reasons, appellants request that the rejection be withdrawn.

F. The Examiner has rejected claims 39 and 42 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the either Markussen reference in view of both of the Grau references.

The Examiner contends that the intermediate disclosed by Grau '332 is the mono-Arg insulin of formula II, and that it would have been *prima facie* obvious to prepare that formula by expressing a DAN molecule encoding min-proinsulin in either bacteria or yeast as taught by Markussen and cleaving that compound with trypsin as taught by Grau '332 and '684. The Examiner alleges that the motivation for such a preparation would be to produce a stable intermediate of insulin for further treatment with carboxypeptidase B so as to produce insulin to treat diabetes and because Grau '332 allegedly teaches that mono-Arg-insulin is resistant to further tryptic degradation, and thus would be a stable intermediate for future insulin formation.

Appellants note that the arguments regarding claims 21 and 33-36 as set forth in VIII B above provide the reasons why this rejection is in error. To recap, it is clear that a B(1-30) chain is not contemplated by Markussen. And, any suggestion to modify the B chain to B30 before the transpeptidation disclosed in Markussen is expressly distinguished by Markussen as not being within the scope of the invention.

Moreover, even if Thr were hypothetically in the X position, Markussen teaches that this Thr is part of the bridging C chain and would, therefore, be excised upon

transpeptidation and then Thr would be inserted into the B30 position. In other words, Thr at the X position is not equivalent to a B(30) Thr. Thus, a modification of Markussen to render the X position equivalent to the B(30) position would destroy the ability of the precursor to be used as contemplated by Markussen in the transpeptidation reaction.

It is well known in the art that there are numerous methods of synthesizing insulin, and that each method in turn results in the production of various intermediate products, some of which are exceptionally stable like the mono-Arg-insulin that Appellants produce. However, the mere fact that Grau discloses mono-Arg-insulin that is stable in crystalline form does not provide motivation to the skilled artisan to convert the mini-proinsulin of Markussen to a mono-Arg-insulin particularly in view of Markussen's requirement that

- (a) its starting material does not have B(30) Thr, and that this starting material is produced in high yield from yeast, and
- (b) its starting material is converted in a transpeptidation step to form a B(30) ester, which in turn is converted to insulin in high yield.

Thus, the Examiner has not provided a logical reason based on the teachings of the prior art disclosures which justifies the combination of Markussen and Grau. Rather, the Examiner's suggested combination appears to only derive from appellant's

disclosure which is improper. Therefore, Appellants respectfully request that this rejection be withdrawn.

## IX. CONCLUSION

In view of the foregoing arguments, Appellants submit that the Examiner's conclusions of obviousness are erroneous. Each of these conclusions rests upon a suggestion to modify the teachings of Markussen in a manner which has been expressly excluded from the Markussen patent. Thus, the prior art does not suggest that the ordinarily skilled artisan should make the B(1-30)-Arg-A(1-21) compound or that the skilled artisan would have a reasonable expectation of success in making such a compound. Moreover, there is no logical reason apparent from positive, concrete evidence of record that justifies the combination of Grau, which teaches stable mono-Arg-insulin with Markussen, which teaches that its starting material does not have a B(30) Threonine residue, that this particular starting material is produced in high yield, and that this starting material is converted in a transpeptidation step to a B(30) ester, which in turn is converted to insulin in high yield.

Furthermore, there would be no reasonable expectation that using trypsin and carboxypeptidase B on the mini-proinsulin would yield human insulin based on the teachings of Grau, since Grau uses these enzymes to cut natural porcine proinsulin which does not have an equivalent splice site as the bridging member in Appellants

Serial No.: 08/402,394  
Attorney Docket No.: 2481.0790-02

claimed fusion protein. Finally, there is no suggestion in the art of record to include the specific bridging member sequence that appellants claim in their fusion protein.

In view of the foregoing, therefore, appellants respectfully request that the Examiner's rejections of all pending claims under 35 U.S.C. § 103(a) be reversed.

Please grant any extensions of time required to enter this Appeal Brief and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

By: Carol P. Einaudi  
Carol P. Einaudi  
Reg. No. 32,220

Rachel H. Townsend  
Rachel H. Townsend  
Reg. No. 41, 443

Dated: October 19, 1999

LAW OFFICES  
FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
300 I STREET, N. W.  
WASHINGTON, D. C. 20005  
202-408-4000